Complete Summary

GUIDELINE TITLE

Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 92-106: hematopoetic cell transplant.

BIBLIOGRAPHIC SOURCE(S)

Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 92-106: hematopoetic cell transplant. Bethesda (MD): Children's Oncology Group; 2006 Mar. 17 p. [84 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 1.2. 2004 Mar.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.
- September 11, 2007, Rocephin (ceftriaxone sodium): Roche informed healthcare professionals about revisions made to the prescribing information

for Rocephin to clarify the potential risk associated with concomitant use of Rocephin with calcium or calcium-containing solutions or products.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Late effects resulting from hematopoietic cell transplantation, with or without graft versus host disease, to treat pediatric malignancies

Effects include dental, dermatologic, gastrointestinal, immunologic, musculoskeletal, ophthalmologic, and reproductive sequelae and secondary malignancies.

Note: These guidelines are intended for use beginning two or more years following the completion of cancer therapy, and provide a framework for ongoing late effects monitoring in childhood cancer survivors; however, these guidelines are not intended to provide guidance for follow-up of the pediatric cancer survivor's primary disease.

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Screening

CLINICAL SPECIALTY

Allergy and Immunology
Dentistry
Dermatology
Endocrinology
Family Practice
Gastroenterology
Infectious Diseases

Internal Medicine
Obstetrics and Gynecology
Oncology
Ophthalmology
Pediatrics
Pulmonary Medicine
Radiation Oncology

INTENDED USERS

Advanced Practice Nurses
Dentists
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide recommendations for screening and management of late effects in survivors of pediatric malignancies
- To increase quality of life and decrease complication-related healthcare costs for pediatric cancer survivors by providing standardized and enhanced follow-up care throughout the life-span that (a) promotes healthy lifestyles, (b) provides for ongoing monitoring of health status, (c) facilitates early identification of late effects, and (d) provides timely intervention for late effects

TARGET POPULATION

Asymptomatic survivors of childhood, adolescent, or young adult cancers who were treated with hematopoietic cell transplantation and who present for routine exposure-related medical follow-up

INTERVENTIONS AND PRACTICES CONSIDERED

Thorough history and physical examination, and screening evaluations

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pertinent information from the published medical literature over the past 20 years (updated as of October 2005) was retrieved and reviewed during the development and updating of these guidelines. For each therapeutic exposure, a complete search was performed via MEDLINE (National Library of Medicine, Bethesda, MD). Keywords included "childhood cancer therapy," "complications," and "late effects," combined with keywords for each therapeutic exposure. References from the bibliographies of selected articles were used to broaden the search.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

"High-level evidence" (recommendation category 1) was defined as evidence derived from high quality case control or cohort studies.

"Lower-level evidence" (recommendation categories 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series, and clinical experience.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The guidelines were scored by the multidisciplinary panel of experts using a modified version of the National Criteria: Comprehensive Cancer Network "Categories of Consensus" system. Each score reflects the expert panel's assessment of the strength of data from the literature linking a specific late effect with a therapeutic exposure, coupled with an assessment of the appropriateness of the screening recommendation based on the expert panel's collective clinical experience. "High-level evidence" (category 1) was defined as evidence derived from high quality case control or cohort studies. "Lower-level evidence" (categories 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series and clinical experience. Rather than submitting recommendations representing major disagreements, items scored as "Category 3" were either deleted or revised by the panel of experts to provide at least a "Category 2B" score for all recommendations included in the guidelines.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In 2002, the leadership of the Children's Oncology Group Late Effects Committee and Nursing Discipline appointed a 7-member task force, with representation from the Late Effects Committee, Nursing Discipline, and Patient Advocacy Committee. The task force was convened to review and summarize the medical literature and develop a draft of clinical practice guidelines to direct long-term follow-up care for pediatric cancer survivors. The task force followed a modified version of the guideline development process established by the National Comprehensive Cancer Network (NCCN), integrating available literature with expert opinion using reiterative feedback loops.

The original draft went through several iterations within the task force prior to initial review. Multidisciplinary experts in the field, including nurses, physicians (pediatric oncologists and other subspecialists), patient advocates, behavioral specialists, and other healthcare professionals, were then recruited by the task force to provide an extensive, targeted review of the draft, including focused review of selected guideline sections. Revisions were made based on these recommendations. The revised draft was then sent out to additional multidisciplinary experts for further review. A total of 62 individuals participated in the review process. The guidelines subsequently underwent comprehensive review and scoring by a panel of experts in the late effects of pediatric malignancies, comprised of multidisciplinary representatives from the COG Late Effects Committee.

Revisions

In order to keep the guidelines current and clinically meaningful, the COG Late Effects Committee organized 18 multi-disciplinary task forces in March 2004. These task forces were charged with the responsibility for monitoring the medical literature in regard to specific system-related clinical topics relevant to the guidelines (e.g., cardiovascular, neurocognitive, fertility/reproductive), providing periodic reports to the Late Effects Committee, and recommending revisions to the guidelines and their associated health education materials and references (including the addition of therapeutic exposures) as new information became available. Task force members were assigned according to their respective areas of expertise and clinical interest. A list of these task forces and their membership is included in the "Contributors" section of the original guideline document. The revisions incorporated into the current release of these guidelines (Version 2.0 – March 2006) reflect the contributions and recommendations of these task forces.

All revisions proposed by the task forces were evaluated by a panel of experts, and if accepted, assigned a score (see "Rating Scheme for the Strength of the Evidence"). Proposed revisions that were rejected by the expert panel were returned with explanation to the relevant task force chair. If desired, task force chairs were given an opportunity to respond by providing additional justification and resubmitting the rejected task force recommendation(s) for further consideration by the expert panel. A total of 34 sections and 9 Health Links were added to Version 2.0 of these guidelines.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Each score relates to the strength of the association of the identified late effect with the specific therapeutic exposure based on current literature, and is coupled with a recommendation for periodic health screening based on the collective clinical experience of the panel of experts. This is due to the fact that there are no randomized clinical trials (and none forthcoming in the foreseeable future) on which to base recommendations for periodic screening evaluations in this population; therefore, the guidelines should not be misconstrued as representing conventional "evidence-based clinical practice guidelines" or "standards of care".

Each item was scored based on the level of evidence currently available to support it. Scores were assigned according to a modified version of the National Comprehensive Cancer Network "Categories of Consensus," as follows:

1 There is uniform consensus of the panel that (1) there is high-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

2A There is uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

2B There is non-uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

3 There is major disagreement that the recommendation is appropriate.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial version of the guidelines (Version 1.0 – Children's Oncology Group Late Effects Screening Guidelines) was released to the Children's Oncology Group (COG) membership in March 2003 for a six-month trial period. This allowed for initial feedback from the COG membership, resulting in additional review and revision of the guidelines by the Late Effects Committee prior to public release.

Revisions

All revisions proposed by the task forces were evaluated by a panel of experts, and if accepted, assigned a score (see "Rating Scheme for the Strength of the Evidence"). Proposed revisions that were rejected by the expert panel were returned with explanation to the relevant task force chair. If desired, task force chairs were given an opportunity to respond by providing additional justification and resubmitting the rejected task force recommendation(s) for further consideration by the expert panel.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendations (1, 2A, 2B, 3) are defined at the end of the "Major Recommendations" field.

Note from the Children's Oncology Group and the National Guideline Clearinghouse (NGC): The *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (COG LTFU) are organized according to therapeutic exposures; this guideline has been divided into individual summaries. In addition to the current summary, the following are available:

- Sections 1-2: Any Cancer Experience
- Sections 3–5: Serum/Blood Products
- Sections 6–37: Chemotherapy
- Sections 38–91: Radiation
- Sections 107–132: Surgery
- Sections 133–136: Other Therapeutic Modalities
- Sections 137–146: Cancer and General Health Screening

In order to accurately derive individualized screening recommendations for a specific childhood cancer survivor using this guideline, see "Using the COG LTFU Guidelines to Develop Individualized Screening Recommendations" in the original guideline document. (Note: For ease of use, a Patient-Specific Guideline Identification Tool has been developed to streamline the process and is included in Appendix I of the original guideline document.)

Guideline Organization

The *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are organized according to therapeutic exposures, arranged by column as follows:

System	Body system (e.g., auditory, musculoskeletal) most relevant to each guideline section.
Score	Score assigned by expert panel representing the strength of data from the literature linking a specific late effect with a therapeutic exposure coupled with an assessment of the appropriateness of the screening recommendation based on collective clinical experience.

Section Number	Unique identifier for each guideline section corresponding with listing in Index.
Therapeutic Agent	Therapeutic intervention for malignancy, including chemotherapy, radiation, surgery, blood/serum products, hematopoietic cell transplant, and other therapeutic modalities.
Risk Factors	Host factors (e.g., age, sex, race, genetic predisposition), treatment factors (e.g., cumulative dose of therapeutic agent, mode of administration, combinations of agents), medical conditions (e.g., pre-morbid or co-morbid conditions), and health behaviors (e.g., diet, smoking, alcohol use) that may increase risk of developing the complication.
Highest Risk Factors	Conditions (host factors, treatment factors, medical conditions and/or health behaviors) associated with the highest risk for developing the complication.
Periodic Evaluations	Recommended screening evaluations, including health history, physical examination, laboratory evaluation, imaging, and psychosocial assessment. Recommendation for minimum frequency of periodic evaluations is based on risk factors and magnitude of risk, as supported by the medical literature and/or the combined clinical experience of the reviewers and panel of experts.
Health Counseling/ Further Considerations	***Health Links***: Health education materials developed specifically to accompany these guidelines. Title(s) of Health Link(s) relevant to each guideline section are referenced in this column. Health Link documents are included in Appendix II of the original guideline document. **Counseling**: Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication. **Resources**: See the original guideline document for lists of books and web sites that may provide the clinician with additional relevant information. **Considerations for Further Testing and Intervention**: Recommendations for further diagnostic evaluations beyond minimum screening for individuals with positive screening tests, recommendations for consultation and/or referral, and recommendations for management of exacerbating or predisposing conditions.
References	References are listed immediately following each guideline section in the original guideline document. Included are medical citations that provide evidence for the association of the therapeutic intervention with the specific treatment complication and/or evaluation of predisposing risk factors. In addition, some general review articles have been included in the Reference section of the original guideline document for clinician convenience.

Note: See the end of the "Major Recommendations" field for explanations of abbreviations included in the summary.

System = SMN
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	C
92	**HCT** **Info Link**: Complications after HCT have multifactorial etiology: prior therapy for primary malignancy; intensity of transplant conditioning; stem cell product (e.g., marrow, cord blood, peripheral stem cells); donor (e.g., autologous, allogeneic, unrelated); quality of donor to recipient match; complication of transplant process (immunosuppression and GVHD); complications in the post-transplant period; underlying disease; host genetic factors; lifestyle behaviors. This section includes late treatment complications that may be observed in HCT recipients not covered elsewhere in these guidelines. Refer to the guidelines listed at the beginning of the	**Acute myeloid leukemia** **Myelodysplasia**	**Treatment Factors** Radiation therapy Stem cell mobilization with etoposide Alkylating agent chemotherapy Epipodophyllotoxins Anthracyclines Autologous transplant	**Host Factors** Older age **Treatment Factors** Autologous transplant for non-Hodgkin's and Hodgkin's lymphoma	**History** **Fatigue** **Bleeding** **Easy bruising** (Yearly up to 10 years after transplant) **Physical** **Dermatologic exam (pallor, petechiae, purpura)** (Yearly up to 10 years after transplant) **Screening** **CBC/differential** (Yearly up to 10 years after transplant)	**H** **S R fi** R R C **C** C pr fa po bo **C fo T In** B ex cl in

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	C
	"Major Recommendations" section for specific details related to late complications of radiation and of specific chemotherapeutic agents.					

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = SMN
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
93	**HCT**	**Solid tumors**	**Host Factors** Younger age at transplant Fanconi's anemia **Treatment Factors** Radiation therapy **Medical Conditions** Hepatitis C infection cGVHD Human papilloma virus infection	**Treatment Factors** TBI	**Physical** **Evaluation for benign or malignant neoplasms** (Yearly)	**Health Links** **See "Patient Resources" field** Reducing the Risk of Second Cancers **Considerations for Further Testing and Intervention** Females with cGVHD appear to be at increased risk for cervical cancer and should, at minimum, have pelvic exams and PAP testing according to ACS recommendations (see Section 138 in the Cancer and

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
			(females)			General Health Screening guideline listed at the beginning of the "Major Recommendations" field) with more aggressive monitoring as clinically indicated. Oncology consultation as clinically indicated.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = SMN
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
94	**HCT**	**Lymphoma**	**Medical Conditions** cGVHD	**Medical Conditions** Chronic hepatitis C with siderosis and steatosis	**Physical** **Lymphadenopathy** **Splenomegaly** (Yearly)	**Considerations for Further Testing and Intervention** Oncology consultation as clinically indicated.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = GI/Hepatic
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
95	**HCT**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload	**Treatment Factors** History of multiple transfusions Radiation to the liver Antimetabolite therapy **Medical Conditions** cGVHD Viral hepatitis History of VOD **Health Behaviors** Alcohol use	**Medical Conditions** Chronic hepatitis C with siderosis and steatosis	**Screening** **ALT** **AST** **Bilirubin** **Ferritin** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **See "Patient Resources" field** Liver Health Gastrointestinal Health **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patient with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Note: *PCR testing for HCV may be required in immunosuppressed patients who are negative for antibody*. Gastroenterology/hepatolog consultation in patients with persistent liver dysfunction or known hepatitis. Hepatiti A and B immunizations in patients lacking immunity. Consider liver biopsy in patients with persistent elevation of ferritin (based on clinical context and magnitude of elevation). Consider phlebotomy or chelation therapy for treatment of iron overload. Consider erythropoietin in patients with iron overload and low hemoglobin.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Musculoskeletal
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseli Further Considerat
96	**HCT**	**Osteonecrosis** **(Avascular Necrosis)** **Info Link**: Osteonecrosis typically occurs during the acute treatment phase, may progress over time or resolve. Multifocal osteonecrosis is significantly more common (3:1) than unifocal.	**Host Factors** Age ≥10 years at time of transplant **Treatment Factors** Corticosteroids (dexamethasone effect is more potent than prednisone) TBI High-dose radiation to any bone Allogeneic HCT >autologous	**Treatment Factors** Prolonged corticosteroid therapy (e.g., for chronic GVHD) **Medical Conditions** cGVHD	**Screening** **Joint pain** **Swelling** **Immobility** **Limited range of motion** (Yearly) **Physical** **Musculoskeletal exam** (Yearly)	**Health Link** **See "Patien Resources' field** Osteonecros **Considerat for Further Testing an Interventic** MRI as clinic indicated in patients with history suggestive o osteonecros (should be d soon after symptom onset). Orthopedic consultation patients with positive ima and/or symptoms o osteonecros Physical the evaluation (non-pharmacolog pain managemen range of motion, strengthenin stretching, functional mobility).

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Musculoskeletal
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Counse Furth Considera
97	**HCT**	**Osteopenia** **Osteoporosis** Osteopenia is defined as BMD ≥1 and <2.5 SD below mean Osteoporosis is defined as BMD ≥2.5 SD below mean **Info Link**: The World Health Organization definition of osteoporosis in adults is based on comparison of a measured BMD of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the YOUNG-NORMAL MEAN BMD. A T-score of	**Host Factors** Both genders are at risk **Treatment Factors** Methotrexate Corticosteroids Cranial radiation **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use	**Host Factors** Older age at time of treatment **Treatment Factors** Prolonged corticosteroid therapy (e.g., for chronic GVHD)	**Screening** **Bone density evaluation** (DEXA or quantitative CT) (Baseline at entry into long-term followup. Repeat as clinically indicated.) **Info Link**: The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. DEXA provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone	**Health Lir** **See "Patie Resources field** Bone Healt **Resources** National Osteoporos Foundation website: www.nof.o **Considera for Furthe Testing ar Intervent** Nutritional supplemen cases of osteopenia unresponsi behavioral dietary manageme Calcium 10 1500 mg d plus RDA f vitamin D. caution regarding calcium supplemen in patients history of r lithiasis. Treatment

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Counse Furth Considera
		≥2.5 standard deviations BELOW the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. There are not defined standards for referral or treatment of low BMD in children.			dimension and density.	exacerbati predisposi conditions hormonal replacemer therapy for hypogonad growth hor deficiency, correction chronic metabolic acidosis th could accel bone loss). Endocrine consultatio patients wi osteoporos history of multiple fractures fo pharmacol interventio (e.g., bisphospho calcitonin, selective estrogen receptor modulators

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

With Chronic GVHD

System = Dermatologic
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
98	**HCT with cGVHD**	**Dermatologic toxicity** Permanent alopecia Nail dysplasia Vitiligo Scleroderma **Info Link**: More common with active cGVHD; effects may persist after cGVHD resolves.			**Physical** **Hair** (alopecia) **Nail** (hypoplasia) **Skin** (vitiligo, scleroderma) (Yearly)	**Health Links** **See "Patient Resources" field** Skin Health

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Ocular
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Counsel Furth Considera
99	**HCT with cGVHD**	**Xerophthalmia (keratoconjunctivitis sicca)** **Info Link:** More common with active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Cranial radiation Eye radiation Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Radiation dose to eye ≥30 Gy Radiation fraction ≥2 Gy	**History** **Dry eyes (burning, itching, foreign body sensation, inflammation)** (Yearly) **Physical**	**Health Lir** **See "Pati Resource field** Eye Health **Considera for Furth Testing a Intervent**

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Counsel Furth Considera
					Eye exam (Yearly)	Supportive with artific tears. Schirmer's testing as clinically indicated. Ongoing ophthalmo follow-up f identified problems. Consider e six month ophthalmo evaluation patients wi corneal damage.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Dental
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
100	**HCT with cGVHD**	**Xerostomia** **Salivary gland dysfunction** **Dental caries** **Periodontal disease** **Oral cancer**	**Treatment Factors** Head and neck radiation involving the parotid gland Higher radiation doses Radiomimetic chemotherapy (e.g.,	**Treatment Factors** Salivary gland radiation dose ≥30 Gy	**History** **Xerostomia** (Yearly) **Physical** **Oral exam** (Yearly) **Screening** **Dental**	**Health Links** **See "Patient Resources" field** Dental Health **Considerations for Further Testing and Intervention** Supportive care

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
		Info Link: More common with active cGVHD; effects may persist after cGVHD resolves.	doxorubicin, dactinomycin)		**exam and cleaning** (Every six months)	with saliva substitutes, moistening agents, and sialogogues (pilocarpine). Regular dental care including fluoride applications and regular screening for intraoral malignancy.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Pulmonary
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Con
101	**HCT with cGVHD**	**Pulmonary toxicity** Bronchiolitis obliterans Chronic bronchitis Bronchiectasis **Info Link**: More common with active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Chest radiation TBI Pulmonary toxic chemotherapy: • Bleomycin • Busulfan • Carmustine (BCNU) • Lomustine (CCNU)	**Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**History** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **Physical** **Pulmonary exam** (Yearly) **Screening**	**Healt** **See "** **Resou** Pulmo **Resou** Extens inform regard cessat availa patien NCI's www.s **Couns** Couns

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Healt Con
					Chest x-ray **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term followup. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	tobacc avoida cessat who d SCUBA be adv medic from a medic **Consi for Fu Testir Interv** In pat abnorr and/or consid evalua genera Pulmo consul patien sympt pulmo dysfur influer Pneum vaccin

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Immune
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	H Cou F Consi
102	**HCT with cGVHD**	**Immunologic complications** Secretory IgA deficiency Hypogammaglobulinemia		**Host Factors** Low CD4 T-cell count	**History** **Chronic conjunctivitis**	**Consid for Fur Testing Interv**

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	H Cou F Consi
		Chronic infections (e.g., conjunctivitis, sinusitis, and bronchitis associated with chronic GVHD) **Info Link**: Related to cGVHD; effects may persist or resolve over time.		**Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**Chronic sinusitis** **Chronic bronchitis** (Yearly) **Physical** **Pulmonary exam** (Yearly) **Screening** **Eye exam** **Nasal exam** **Pulmonary exam** (Yearly)	Conside anti-fur prophyl patients cGVHD of immun therapy Immun infectio consult assistar manage chronic

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Immune
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health C Fu Consid
103	**HCT with cGVHD**	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., Haemophilus	**Treatment Factors** Splenic radiation Ongoing immuno-suppression	**Host Factors** Hypogammaglobulinemia	**Physical** **Physical exam at time of febrile illness to evaluate degree of illness**	**Health Lin** **See "Patie Resources** Splenic pre **Considera Further Te Interventi**

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health C Fu Consid
		influenzae, streptococcus pneumoniae, meningococcus) **Info Link**: This section applies only to patients who have active cGVHD			**and potential source of infection** (When febrile T ≥101 degrees F) **Screening** **Blood culture** (When febrile T ≥101 degrees F)	Consider a prophylaxis encapsulat and bacteremia prophylaxis of immuno therapy for patients wi degrees F (degrees C) signs of se administer acting, bro parenteral (e.g., ceftr continue cl monitoring awaiting bl results. Ho and broade antimicrobi (e.g., addit vancomycin necessary circumstan the presen leukocytosi neutropeni significant baseline CB clinical app fever ≥104 meningitis, or other se of infection septic shoc previous hi serious infe Immunize Pneumococ Meningoco vaccines. P booster in years old a after previ

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = GI/Hepatic
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
104	**HCT with cGVHD**	**Esophageal stricture** **Info Link**: Related to cGVHD; generally not reversible over time.	**Treatment Factors** Radiation involving the esophagus Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Gastroesophageal reflux	**Treatment Factors** Radiation dose ≥40 Gy	**History** **Dysphagia** **Heartburn** (Yearly)	**Health Links** **See "Patient Resources" field** Gastrointestinal Health **Considerations for Further Testing and Intervention** Surgery and/or gastroenterology consultation for symptomatic patients.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Female reproductive
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
105 (Female)	**HCT with cGVHD**	**Vaginal fibrosis/stenosis** **Info Link**: Related to cGVHD; generally not reversible over time.	**Treatment Factors** Pelvic radiation		**History** **Psychosocial assessment** **Dyspareunia** **Vulvar pain**	**Considerations for Further Testing and Intervention** Gynecologic consultation for management. Psychological

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
					Post-coital bleeding **Difficulty with tampon insertion** (Yearly)	consultation in patients with emotional difficulties.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

System = Musculoskeletal
Score = 1

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
106	**HCT with cGVHD**	**Joint contractures** **Info Link**: Related to cGVHD; generally not reversible over time.			**Physical** **Musculoskeletal exam** (Yearly)	**Considerations for Further Testing and Intervention** Consultation with physical therapy, rehabilitation medicine/physiatrist.

Note: See a list of Abbreviations at the end of the "Major Recommendations" field.

Abbreviations

- ACS, American Cancer Society
- ALT, alanine aminotransferase
- AST, aspartate aminotransferase
- BMD, bone mineral density
- cGVHD, chronic graft versus host disease
- CBC, complete blood count
- CT, computed tomography
- CXR, chest x-ray
- DEXA, dual energy x-ray absorptiometry
- DLCO, diffusion capacity of carbon monoxide
- DOE, dyspnea on exertion
- GI, gastrointestinal

- GVHD, graft versus host disease
- Gy, gray
- HCT, hematopoietic cell transplant
- HCV, Hepatitis C virus
- HIB, Haemophilus influenza b vaccine
- IgA, immunoglobulin A
- MRI, magnetic resonance imaging
- NCI, National Cancer Institute
- PCP, *Pneumocystis carinii* pneumonia
- PCR, polymerase chain reaction
- PFTs, pulmonary function tests
- RDA, recommended daily allowance
- SD, standard deviation
- SMN, secondary malignant neoplasm
- SOB, shortness of breath
- T, temperature
- TBI, total body irradiation
- VOD, veno-occlusive disease

Definitions:

Explanation of Scoring for the Long-Term Follow-Up Guidelines

1 There is uniform consensus of the panel that (1) there is high-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

2A There is uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

2B There is non-uniform consensus of the panel that (1) there is lower-level evidence linking the late effect with the therapeutic exposure, and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.

3 There is major disagreement that the recommendation is appropriate.

Rating Scheme for the Strength of the Evidence

"High-level evidence" (recommendation category 1) was defined as evidence derived from high quality case control or cohort studies.

"Lower-level evidence" (recommendation categories 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series, and clinical experience.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

Although several well-conducted studies on large populations of childhood cancer survivors have demonstrated associations between specific exposures and late effects, the size of the survivor population and the rate of occurrence of late effects does not allow for clinical studies that would assess the impact of screening recommendations on the morbidity and mortality associated with the late effect. Therefore, scoring of each exposure reflects the expert panel's assessment of the level of literature support linking the therapeutic exposure with the late effect coupled with an assessment of the appropriateness of the recommended screening modality in identifying the potential late effect based on the panel's collective clinical experience.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Potential benefits of implementing these guidelines into clinical practice include earlier identification of and intervention for late onset therapy-related complications in this at-risk population, potentially reducing or ameliorating the impact of late complications on the health status of survivors. In addition, ongoing healthcare that promotes healthy lifestyle choices and provides ongoing monitoring of health status is important for all cancer survivors.

POTENTIAL HARMS

Potential harms of guideline implementation include increased patient anxiety related to enhanced awareness of possible complications, as well as the potential for false-positive screening evaluations, leading to unnecessary further workup. In addition, costs of long-term follow-up care may be prohibitive for some patients, particularly those lacking health insurance, or those with insurance that does not cover the recommended screening evaluations.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The information and contents of each document or series of documents made available by the Children's Oncology Group relating to late effects of cancer treatment and care or containing the title "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" or the title "Health Link," whether available in print or electronic format (including any digital format, e-mail transmission, or download from the website), shall be

known hereinafter as "Informational Content." All Informational Content is for informational purpose only. The Informational Content is not intended to substitute for medical advice, medical care, diagnosis, or treatment obtained from a physician or healthcare provider.

- *To cancer patients (if children, their parents or legal guardians)*: Please seek the advice of a physician or other qualified healthcare provider with any questions you may have regarding a medical condition and do not rely on the Informational Content. The Children's Oncology Group is a research organization and does not provide individualized medical care or treatment.
- *To physicians and other healthcare providers*: The Informational Content is not intended to replace your independent clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of childhood cancer treatment. Neither is the Informational Content intended to exclude other reasonable alternative follow-up procedures. The Informational Content is provided as a courtesy, but not intended as a sole source of guidance in the evaluation of childhood cancer survivors. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.
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- Ultimately, as with all clinical guidelines, decisions regarding screening and clinical management for any specific patient should be individually tailored, taking into consideration the patient's treatment history, risk factors, co-morbidities, and lifestyle. These guidelines are therefore not intended to replace clinical judgment or to exclude other reasonable alternative follow-up procedures. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation of these guidelines is intended to standardize and enhance follow-up care provided to survivors of pediatric malignancies throughout the lifespan. Considerations in this regard include the practicality and efficiency of applying

these broad guidelines in individual clinical situations. Studies to address guideline implementation and refinement are a top priority of the Children's Oncology Group (COG) Late Effects Committee, and proposals to study feasibility of guideline use in limited institutions are currently underway. Issues to be addressed include description of anticipated barriers to application of the recommendations in the guidelines and development of review criteria for measuring changes in care when the guidelines are implemented. Additional concerns surround the lack of current evidence establishing the efficacy of screening for late complications in pediatric cancer survivors. While most clinicians believe that ongoing surveillance for these late complications is important in order to allow for early detection and intervention for complications that may arise, development of studies addressing the efficacy of this approach is imperative in order to determine which screening modalities are optimal for asymptomatic survivors.

In addition, the clinical utility of this lengthy document has also been a top concern of the COG Late Effects Committee. While recognizing that the length and depth of these guidelines is important in order to provide clinically-relevant, evidence-based recommendations and supporting health education materials, clinician time limitations and the effort required to identify the specific recommendations relevant to individual patients have been identified as barriers to their clinical application. Therefore, the COG Late Effects Committee is currently partnering with the Baylor School of Medicine in order to develop a web-based interface, known as "Passport for Care," that will generate individualized exposure-based recommendations from these guidelines in a clinician-focused format for ease of patient-specific application of the guidelines in the clinical setting. As additional information regarding implementation of the Passport for Care web-based interface becomes available, updates will be posted at www.survivorshipguidelines.org.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Patient Resources
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Sections 92-106: hematopoetic cell transplant. Bethesda (MD): Children's Oncology Group; 2006 Mar. 17 p. [84 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Sep (revised 2006 Mar)

GUIDELINE DEVELOPER(S)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All Children's Oncology Group (COG) members have complied with the COG conflict of interest policy, which requires disclosure of any potential financial or other conflicting interests.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 1.2. 2004 Mar.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Children's Oncology Group Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Instructions for use. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 2.0. Children's Oncology Group. 2006 March. 6 p.
- Introductory material. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 2.0. Children's Oncology Group. 2006 March. 9 p.
- Summary of cancer treatment. Appendix I: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 2.0. Children's Oncology Group. 2006 March.
- Patient-specific guideline identification tool. Appendix I: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 2.0. Children's Oncology Group. 2006 March.

Electronic copies: Available in Portable Document Format (PDF) from the Children's Oncology Group Web site.

PATIENT RESOURCES

In an effort led by the Nursing Clinical Practice Subcommittee, complementary patient education materials (*Health Links*) were developed and are available in Appendix II of the original guideline document. The following Health Links are relevant to this summary:

Sections 92, 93

- Reducing the Risk of Second Cancers

Section 95

- Liver Health

Sections 95, 104

- Gastrointestinal Health

Section 96

- Osteonecrosis

Section 97

- Bone Health

Section 98

- Skin Health

Section 99

- Eye Health

Section 100

- Dental Health

Section 101

- Pulmonary Health

Section 103

- Splenic Precautions

NGC STATUS

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